General

Guideline Title

British Association of Dermatologists' guidelines for the safe and effective prescribing of azathioprine 2011.

Bibliographic Source(s)

Meggitt SJ, Anstey AV, Mohd Mustapa MF, Reynolds NJ, Wakelin S. British Association of Dermatologists' guidelines for the safe and effective prescribing of azathioprine 2011. Br J Dermatol. 2011 Oct;165(4):711-34. [183 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Anstey AV, Wakelin S, Reynolds NJ, British Association of Dermatologists Therapy, Guidelines and Audit Subcommittee. Guidelines for prescribing azathioprine in dermatology. Br J Dermatol 2004 Dec;151(6):1123-32.

Recommendations

Major Recommendations

Definitions for the levels of evidence (1++, 1+, 1-, 2++, 2+, 2-, 3, 4) and strength of recommendations (A-D) are presented at the end of the "Major Recommendations" field.

Unlicensed Indications for Azathioprine

There is evidence to support the use of azathioprine outside its product license for the following indications:

- Atopic eczema (Strength of Recommendation A; Level of Evidence 1+)
- Maintenance therapy for Wegener's granulomatosis (Strength of Recommendation B; Level of Evidence 1+)
- Behçet disease (Strength of Recommendation B; Level of Evidence 1+)
- Bullous pemphigoid (Strength of Recommendation B; Level of Evidence 1)

Thiopurine Methyltransferase (TPMT) and Azathioprine Toxicity

- There is strong evidence that baseline testing predicts severe neutropenia in patients with absent TPMT activity (Strength of Recommendation A; Level of Evidence 1+).
- There is good evidence that intermediate TPMT activity is associated with myelotoxicity in patients receiving conventional azathioprine doses (Strength of Recommendation B; Level of Evidence 2++).
- TPMT testing only identifies a proportion of individuals at increased risk of haematological toxicity, hence the continued need for regular

monitoring of blood counts irrespective of TPMT status (Strength of Recommendation B; Level of Evidence 2++).
- TPMT screening should not be declined by healthcare providers on the basis of cost-effectiveness (Strength of Recommendation B; Level of Evidence 2++).

Managing Nausea

(Strength of Recommendation D; Level of Evidence 4)

- Early, mild nausea is a common and often self-limiting side effect of azathioprine.
- Gradual dose escalation may be useful in minimizing initial nausea.
- Moderate nausea can be managed by:
  - Using divided daily doses
  - Taking azathioprine after food
  - Temporary dose reduction
  - Antiemetics
- Nausea associated with other symptoms such as fever, myalgia or arthralgia suggests hypersensitivity and should be managed differently (see section 9.12 in the original guideline document for managing hypersensitivity).

Managing Varicella Zoster Virus (VZV) in Patients Receiving Azathioprine (Ahmed et al., 2007)

(Strength of Recommendation D; Level of Evidence 4)

- Consider temporary withdrawal of azathioprine.
- Prompt use of oral antivirals (aciclovir, valaciclovir or famciclovir) in all patients
- Intravenous antiviral therapy desirable for disseminated or ophthalmic VZV

Managing Hepatotoxicity

(Strength of Recommendation B; Level of Evidence 2++)

- Mild derangement of liver blood tests is not uncommon and may not require alteration of therapy.
- Various patterns of serious liver injury can more rarely be seen at any stage of azathioprine therapy.
- Detection of any abnormal liver blood tests should prompt both careful evaluation and increased frequency of repeat testing; dose reduction or drug withdrawal may be needed.

Azathioprine Dosing

- Patients with normal TPMT activity are at low risk of profound neutropenia and can be prescribed azathioprine at conventional doses (see Table 2 in the original guideline document) (Strength of Recommendation A; Level of Evidence 1+).
- Patients with intermediate (heterozygous) range TPMT activity treated with conventional thiopurine doses have an increased risk of neutropenia and should receive a lower azathioprine maintenance dose (see Table 2 in the original guideline for suggested dose regimen) (Strength of Recommendation C; Level of Evidence 2+).
- Patients with absent TPMT activity (TPMT null) treated with conventional azathioprine doses are at very high risk of profound neutropenia and should in general not be prescribed azathioprine (Strength of Recommendation A; Level of Evidence 1+).
- Side-effects such as dose-dependent nausea may be minimized by building up to the recommended maintenance dose over the first few weeks of therapy (Strength of Recommendation D; Level of Evidence 4).

Baseline TPMT Activity

- TPMT activity should be checked in all patients prior to receiving azathioprine (Strength of Recommendation A; Level of Evidence 1+).
- Clinicians should ensure they take into account differences in TPMT activity reporting practices across the U.K., in order to be certain of the likely genotypic group of their patients (Strength of Recommendation D; Level of Evidence 4).
- TPMT genotyping is only required for patients with indeterminate phenotype (i.e., borderline values) or those who have had a recent blood transfusion (Strength of Recommendation D; Level of Evidence 4).

Toxicity Monitoring

(Strength of Recommendation D; Level of Evidence 4)

- Regular monitoring of liver blood tests and full blood count are required for the duration of therapy.

- Once a patient is stable on a fixed dose of azathioprine monitoring should occur at least 3 monthly.
- Prior to stabilization, monitoring bloods should be performed more frequently.

Benefits of Combined Allopurinol and Azathioprine Therapy

- There is good evidence from nondermatological diseases linking thioguanine nucleotide (TGN) levels to toxicity and therapeutic response (Strength of Recommendation A; Level of Evidence 1+).
- Measurement of metabolites including TGN should be included in future research studies of azathioprine, in order to assess their usefulness in optimizing dosimetry in the clinical setting (Strength of Recommendation D; Level of Evidence 4).

Definitions:

Levels of Evidence

Level of Evidence	Type of Evidence
1++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias*
2++	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal*
3	Nonanalytical studies (for example, case reports, case series)
4	Expert opinion, formal consensus

*Studies with a level of evidence '-' should not be used as a basis for making a recommendation.

Strength of Recommendation

Class	Evidence
A	• At least one meta-analysis, systematic review, or randomized controlled trial (RCT) rated as 1++, and directly applicable to the target population or • A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results or • Evidence drawn from a National Institute for Health and Clinical Excellence (NICE) technology appraisal
B	• A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results, or • Extrapolated evidence from studies rated as 1++ or 1+
C	• A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results, or • Extrapolated evidence from studies rated as 2++

Class	Evidence
C	• Evidence level 3 or 4, or • Extrapolated evidence from studies rated as 2+ or • Formal consensus
D (GPP)	• A good practice point is a recommendation for best practice based on the experience of the guideline development group

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Autoimmune and inflammatory skin diseases, including:

- Systemic lupus erythematosus
- Dermatomyositis
- Pemphigus vulgaris
- Atopic dermatitis
- Psoriasis
- Bullous pemphigoid
- Chronic actinic dermatitis
- Pyoderma gangrenosum
- Pityriasis rubra pilaris
- Wegener's granulomatosis
- Cutaneous vasculitis

Guideline Category

Assessment of Therapeutic Effectiveness

Counseling

Management

Risk Assessment

Treatment

Clinical Specialty

Dermatology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

- To provide up-to-date, evidence-based recommendations for the safe and effective use of azathioprine
- To update and expand on the previous guidelines by (i) offering a complete reappraisal of all relevant literature since 1966 and focusing on key developments over the past 5 years, in particular the applicability of thiopurine methyltransferase (TPMT) assessment to the clinical setting; (ii) addressing important, practical clinical questions relating to the primary guideline objective; (iii) providing guideline recommendations with an evaluation of their health economic impact; and (iv) discussing potential developments and future directions
- To present a detailed review with highlighted recommendations for practical use in the clinic, in addition to updated patient information

Target Population

Patients in the United Kingdom who are treated with azathioprine for autoimmune and inflammatory skin diseases

Interventions and Practices Considered

1. Pretreatment thiopurine methyltransferase (TMPT) measurement
2. TPMT genotyping in patients with indeterminate phenotype
3. Azathioprine doses and dose adjustments
4. Monitoring for toxicity, including full blood counts (FBCs) and renal and liver tests
5. Management of toxicity, including nausea, varicella zoster virus infection, and hepatotoxicity
6. Therapeutic drug monitoring
7. Obtaining informed consent regarding risks of azathioprine, including risk of malignancy

Major Outcomes Considered

- Morbidity and mortality from adverse drug reactions, including susceptibility to infection and toxicity
- Remission induction and maintenance
- Association of marker activity, such as thiopurine methyltransferase (TPMT), in predicting adverse outcomes

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

PubMed, MEDLINE and EMBASE databases were searched up to January 2011 for randomized and nonrandomized controlled clinical trials, case series, case reports, open studies and research articles involving azathioprine and 6-mercaptopurine (6-MP). Due to the expected high number of results in the EMBASE search, which has a particular emphasis on drug literature, additional search protocols were used specifically to target key areas such as thiopurine-metabolizing enzymes and toxicity, as well as separating the results into predominantly dermatology- and gastroenterology-based publications. Literature search terms and strategies are available as an Appendix (see the "Availability of Companion Documents" field).

Searches were also carried out in the Cochrane, National Institute of Health and Clinical Excellence (NICE), Database of Uncertainties about the Effects of Treatments (DUET) and Royal College of Physicians (RCP) databases. Additional relevant references were also isolated from citations in reviewed literature, as well as independent targeted searches carried out by each co-author.

All titles in the English language were screened, and those relevant for first-round inclusion were selected for further scrutiny; the abstracts were then reviewed by all members of the working group and the full papers of relevant material were obtained following selection by common agreement. Specific selection criteria were not deemed necessary as the number of selected abstracts was relatively small (<150) and there was consensus that the full papers were needed in most cases.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence

Level of Evidence	Type of Evidence
1++	High-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
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3	Nonanalytical studies (for example, case reports, case series)
4	Expert opinion, formal consensus

*Studies with a level of evidence '-' should not be used as a basis for making a recommendation.

Methods Used to Analyze the Evidence

Systematic Review

Description of the Methods Used to Analyze the Evidence

Not stated

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The guideline working group consisted of dermatologists and a patient representative.

This set of guidelines has been developed using the British Association of Dermatologists (BAD) recommended methodology and with reference to the Appraisal of Guidelines Research and Evaluation (AGREE) instrument. Recommendations were developed for implementation in the National Health Service (NHS) using a process of considered judgment based on the evidence.

The structure of the guidelines was discussed and different co-authors were allocated separate subsections. Each co-author then performed a detailed appraisal of the relevant literature, and all subsections were subsequently collated and edited to produce the final guideline.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendation

Class	Evidence
A	• At least one meta-analysis, systematic review, or randomized controlled trial (RCT) rated as 1++, and directly applicable to the target population or • A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results or • Evidence drawn from a National Institute for Health and Clinical Excellence (NICE) technology appraisal
B	• A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results, or • Extrapolated evidence from studies rated as 1++ or 1+
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D	• Evidence level 3 or 4, or • Extrapolated evidence from studies rated as 2+ or • Formal consensus
D (GPP)	• A good practice point is a recommendation for best practice based on the experience of the guideline development group

Cost Analysis

Health Economics

Cost of Drug

Azathioprine is relatively inexpensive compared with other immunosuppressive drugs used by dermatologists such as ciclosporin and mycophenolate mofetil. Expressed in relative terms, the daily cost of ciclosporin or mycophenolate mofetil in the doses used in dermatology is up to

20 times as great as the daily cost of azathioprine.

Cost of Thiopurine Methyltransferase Testing

Thirty years after the initial publication by Weinshilboum and Sladek on the genetics of thiopurine methyltransferase (TPMT) inheritance, the measurement of red cell TPMT activity is now a routine test in the U.K. (details of biochemistry laboratories offering TPMT measurement are given in Appendix 2 in the original guideline document). Due to the high volume of demand, and high throughput in the laboratories, the cost for this assay is so low that there is no longer a credible argument to be made against testing on the basis of cost. Furthermore, the turnaround time (i.e., delay between ordering the test and receiving the result) is stated to be 24 hours in the U.K. biochemistry department with the highest throughput of TPMT assays. The current charge for TPMT testing is around £30; this cost may fall with further refinements to testing methodology. The current cost of TPMT screening in the U.K. is low compared with other countries, which is partly explained by economies of scale that have resulted from widespread uptake of this assay by prescribing doctors.

Cost-Effectiveness of Thiopurine Methyltransferase Testing

A recent systematic review of the health economics of azathioprine-related TPMT screening identified seven relevant studies. These had many shortcomings, but the review concluded that attempts to identify TPMT deficiency prior to prescribing azathioprine had a modest cost that overall was essentially cost neutral. Unfortunately, despite the availability of the TPMT enzyme assay, new cases of azathioprine-induced pancytopenia in patients where baseline TPMT status was not established continue to be reported. These cases emphasize the risk to life and high cost of the intensive supportive care needed for patients with severe and prolonged myelosuppression. Collectively, these cases appear to make a watertight case for routine pretreatment TPMT measurement, and as TPMT testing in the U.K. is becoming an increasingly inexpensive test, previous health economic arguments are now of limited relevance. This is further highlighted by a case of severe neutropenia (TPMT null) that developed in the nonscreened arm of the Department of Health-funded TARGET study which was set up to address the utility of pharmacogenetic testing in the National Health Service.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The draft document was circulated to the British Association of Dermatologists (BAD) membership, the British Dermatological Nursing Group (BDNG), an immunologist and a hepatologist for comments and peer reviewed by the Clinical Standards Unit of the BAD (made up of the Therapy & Guidelines and Audit & Clinical Standards Subcommittees) prior to publication.

Evidence Supporting the Recommendations

References Supporting the Recommendations

Ahmed AM, Brantley JS, Madkan V, Mendoza N, Tyring SK. Managing herpes zoster in immunocompromised patients. Herpes. 2007 Sep;14(2):32-6. [35 references] PubMed

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Remission of certain dermatological disorders
- Prevention of adverse effects associated with azathioprine through pretreatment assessment and toxicity monitoring

Potential Harms

A widely experienced and important problem for the clinician using azathioprine is the large variability demonstrated by patients both in response to the drug and side-effects. In some patients this can be explained by increasingly well-characterized genetic differences in drug-metabolizing enzymes, but the role of other potential factors such as variability in drug absorption and bioavailability remains a matter for speculation. Adverse effects include:

Short-term toxicity

- Nausea
- Hypersensitivity

Medium-term toxicity

- Myelotoxicity
- Susceptibility to infection
- Hepatotoxicity

Long-term toxicity

- Carcinogenesis
- Nonmelanoma skin cancer
- Lymphoma

See the original guideline document for full discussion of risk factors and specific drug interactions associated with adverse events.

Care should be taken with use of azathioprine in the elderly; the summary of product characteristics (SPC) recommends that additional care should be taken with haematological monitoring and that doses used should be at the lower end of the recommended range.

Contraindications

Contraindications

- There are few absolute contraindications to the use of azathioprine, but those listed in the manufacturer's data sheet are hypersensitivity to azathioprine/6-mercaptopurine (6-MP), severe infections, severely impaired hepatic or bone marrow function, pancreatitis, live vaccines, pregnancy unless benefits outweigh risks, lactation.
- In hypersensitive patients, desensitization to azathioprine and 6-MP has been successfully attempted, but this cannot be recommended as its safety is unproven. Pregnancy is a relative contraindication and women taking azathioprine are advised to not breastfeed their infants, although more recent data suggest this may be safe. It is not usually recommended that azathioprine is initiated or continued in patients with known malignancy, as immunosuppression may increase the risk of disease progression.
- There are also several relative contraindications to azathioprine use that are not included in the summary of product characteristics (SPC). Discussion of the following issues is covered in section 10 of the original guideline: (i) renal impairment; (ii) viral hepatitis; (iii) human immunodeficiency virus (HIV) infection; (iv) previous varicella zoster virus exposure; (v) premalignancy.

Qualifying Statements

Qualifying Statements

This document has been prepared on behalf of the British Association of Dermatologists (BAD) and is based on the best data available when the document was prepared. It is recognized that under certain conditions it may be necessary to deviate from the guidelines, and that the results of future studies may require some of the recommendations herein to be changed. Failure to adhere to these guidelines should not necessarily be considered negligent, nor should adherence to these recommendations constitute a defence against a claim of negligence.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Audit Criteria/Indicators

Patient Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Meggitt SJ, Anstey AV, Mohd Mustapa MF, Reynolds NJ, Wakelin S. British Association of Dermatologists' guidelines for the safe and effective prescribing of azathioprine 2011. Br J Dermatol. 2011 Oct;165(4):711-34. [183 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2004 Dec (revised 2011 Oct)

Guideline Developer(s)

British Association of Dermatologists - Medical Specialty Society

Source(s) of Funding

British Association of Dermatologists

Guideline Committee

British Association of Dermatologists Therapy and Guidelines Subcommittee and the Audit and Clinical Standards Subcommittee (Clinical Standards Unit)

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

N.J. Reynolds receives research grant support from Stiefel, a GSK Company, through a Knowledge Transfer Partnership Award and AstraZeneca through a BBSRC CASE award, and sat on advisory boards (nonpersonal) for Abbott, Janssen-Cilag, Schering-Plough and Creabilis Therapeutics.

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Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the British Association of Dermatologists Web site .

Availability of Companion Documents

The following is available:

- Bell HK, Ormerod AD. Writing a British Association of Dermatologists' clinical guideline: an update on the process and guidance for

authors. Br J Dermatol 2009;160:725–8. Electronic copies: Available in Portable Document Format (PDF) from the British Association of Dermatologists (BAD) Web site .

Literature search strategies are available from the BAD Web site .

Recommended audit points are provided in section 14 of the original guideline document .

Patient Resources

The following is available:

- Azathioprine. Patient information leaflet. London (England): British Association of Dermatologists; 2010 May. 3 p. Electronic copies: Available in Portable Document Format (PDF) from the British Association of Dermatologists Web site .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on August 19, 2008. The information was verified by the guideline developer on September 15, 2008. The information is being reviewed for currency by the guideline developer and updated by ECRI Institute on March 12, 2010. This NGC summary was updated by ECRI Institute on August 27, 2012. The updated information was verified by the guideline developer on October 12, 2012.

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